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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/029,471	10/25/2001	Mehran M. Khodadoust	50638/013001	6131

21559 7590 12/14/2009

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ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
12/14/2009	ELECTRONIC

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/029,471
Filing Date: October 25, 2001
Appellant(s): KHODADOUST, MEHRAN M.

Paul Clark
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed September 9, 2009 appealing from the Office action mailed September 10, 2007.

The prior answer dated October 30, 2008 is vacated. This supplemental answer replaces all prior answers and is based on the Appeal Brief filed to correct the real party of interest, filed since the mailing of the examiner's answer dated 30 Oct 2008.

(1) Real Party in Interest

The real party in interest in this case is Bionaut Pharmaceuticals Inc., to whom all interest in the present application has been assigned.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,922,601	Baetscher	7-1999
6,436,707	Zambrowicz	8-2002

Massie et al. "Inducible Overexpression of a Toxic Protein by an Adenovirus Vector with a Tetracycline-Regulatable Expression Cassette" J. of Virology, vol. 72, no. 3 (1998), pp. 2289-2296

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 83, 84, 88-96, 98-104 and 107-108 stand rejected under 35 U.S.C. 102(b) as being anticipated by Baetscher et al (U.S. 5,922,601).

The following rejections are based on the following interpretation of the term "reporter." Absent an explicit definition to the contrary, a "reporter" is any polypeptide sequence (as encoded by a polynucleotide sequence) that can be detected by conventional means. This includes colorimetric assays, bio- or chemiluminescence assays, as well as screening assays such as selection on a particular growth medium (such as a positive or negative selection marker). Because any polypeptide sequence can be detected by some means (e.g., by measuring its enzymatic activity, or detecting it with specific antibodies), any polypeptide meets the limitation of being a "reporter."

Baetscher et al teach a gene trap nucleic acid construct comprising the following elements in a 5'-to-3' orientation:

Splice acceptor---IRES---Neo-HSV-TK (see for example Figure 2).

Because the Neomycin resistance gene is a positive selection marker and HSV-TK is a negative selection marker the above specific construct teaches the following general formula:

Splice acceptor---IRES---positive selection---negative selection.

This nucleic acid construct is then placed within the context of a retroviral vector construct (see for example column 12, lines 34-55), which along with LTR elements (i.e., integration sequences) additionally contains selectable or assayable markers, including those useful in "fluorescence activated cell sorting" (see for example column 8,

lines 50-57). Thus, the general formula of the nucleic acid construct taught by Baetscher et al has the overall general formula of:

Splice acceptor---IRES---positive selection---negative selection---reporter.

In order to get expression of the reporter, a promoter element must be operatively linked to the reporter gene. Thus, the construct taught by Baetscher et al can further be visualized as having the following general formula:

Splice acceptor---IRES---positive selection---negative selection---STOP---Promoter---reporter.

Importantly, as set forth above, the retroviral vector further comprises selectable or assayable markers, including those useful in "fluorescence activated cell sorting" (see for example column 8, lines 50-57). Such a reporter can be a "protein that spontaneously emits light…Green Fluorescent Protein (GFP)" (see for example column 10, lines 12-19).

Notably, the Neo-HSV-Tk marker is not operably linked to a promoter within the context of the nucleotide construct; i.e., it is a promoterless marker construct (see for example column 5, lines 44-67). As a result, the selection markers are only expressed when the construct integrates into the genome of a host cell, and the selection markers become operably linked to an endogenous promoter element of the host cell (see for example column 13, lines 25-33). Thus, Baetscher et al also teach a host cell comprising the claimed nucleic acid constructs/vectors.

Finally, Baetscher et al teach a particular vector having the following formula:

Splice acceptor---IRES---Neo-HSV-TK---STOP---Promoter---Ampicillin.

Support for such a vector comes both from the above analysis of the teachings, and from column 12, lines 63-67, which indicate that the retroviral vector of the element can contain "regulatory elements suitable for propagation and selection in *E. coli*." This includes the Ampicillin resistance gene, which can serve as a positive selection marker (in the presence of ampicillin), and a prokaryotic promoter (i.e., regulatory element) to allow the expression of the Ampicillin resistance gene. Furthermore, given the interpretation of a reporter molecule set forth above, the Neomycin resistance gene can also be a reporter, allowing for the following formula:

Splice acceptor---IRES---reporter---negative marker---STOP---Promoter---positive marker.

In conclusion, Baetscher et al meets all of the limitations of the newly added claims, and therefore anticipates the claimed invention.

Claim Rejections - 35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 85 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher et al in view of MPEP § 2144.04 (VI)(C).

Baetscher et al teach all of the elements set forth above in the rejection under 35 USC § 102(b); this includes all of the specific elements set forth as limitations in each

embodiment of the instant claims. However, Baetscher et al do not specifically teach the different orientations as set forth in each embodiment of the claims. Although Baetscher et al teach the presence of each element set forth in claim 85, they do not set forth the specific order. It is simply that a different order of the elements is used.

MPEP § 2144.04 (VI)(C) cites that the rearrangement of parts is an obvious matter of design choice, unless the variation modifies the operation of the device. In the instant case, the particular elements set forth in the claimed nucleic acids are not indicated as altering the function of the claimed nucleic acids based upon their positioning. Indeed, the specification teaches that each nucleic acid is to be used for the same function, the generation of a library of cells under the control of specific regulatory elements (see pages 5-6 of the instant specification). Because each of the nucleic acids set forth in the claims have the same elements and the same function, it would be obvious for the ordinary skilled artisan to alter the sequence of the elements within the nucleic acids as a matter of design choice. This is merely an aesthetic choice, and confers no patentable functional distinction on the vectors (based on the instant disclosure). The ordinary skilled artisan would have been motivated to alter the sequence of the elements within the nucleic acids because the function of each element is the same as in the particular orientation taught by Baetscher et al, and such rearrangements have been determined to be patentably equivalent. Absent evidence to the contrary (i.e., some teaching in the instant specification indicating that each particular order of elements confers a patentably distinct function on the claimed nucleic acids), the ordinary skilled artisan would have had a reasonable expectation of success

when altering the order of the elements taught by Baetscher et al to arrive at each of the claimed embodiments of the invention.

Claims 87 and 106 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher et al in view of Zambrowicz *et al.* (US 6,436,707; see entire document.)

Baetscher et al teach all of the elements set forth above. Briefly, Baetscher teaches the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders. However, Baetscher et al do not teach the specific use of recombinase sequences in their nucleic acids.

Zambrowicz et al teach the construction of gene trap vectors (see for example the Abstract, column 2, lines 10-31), comprising many of the elements set forth in the teachings of Baetscher et al such as splice acceptor sites, IRES elements and positive/negative selectable marker genes. Zambrowicz et al also teach the use of recombinase sites within the gene trap cassette (see for example column 8, lines 40-55), and indicates that these sites have the advantage of allowing the conditional activation or deactivation of the gene trap (see for example column 10, lines 22-30).
It would have been obvious for the ordinary skilled artisan to combine the teachings of Baetscher et al and Zambrowicz et al to arrive at the instantly claimed nucleic acids because the teachings both concern the making and using of gene trap vectors, and thus are clearly combinable. The ordinary skilled artisan would have been motivated to combine the teachings of Baetscher et al and Zambrowicz et al to utilize recombinase sites because Zambrowicz et al clearly teach the advantage of being able to turn on and

off the gene trap mechanism using said sites. Absent evidence to the contrary, the ordinary skilled artisan would have had a reasonable expectation of success when combining the teachings of Baetscher et al and Zambrowicz et al.

Claims 86, 97-105 and 107-109 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Baetscher et al in view of Massie et al.

Baetscher et al teach all of the elements set forth above. Briefly, Baetscher et al teach the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders. However, Baetscher et al do not teach a transactivator incorporated into a cassette or vector, specifically, they do not teach the transactivator being a tetracycline regulator (tTA).

Massie et al (J. of Virology, 72 (3): 2289-2296, 1998, specifically p. 2289, Materials & Methods and 2295) teach a cassette and then a vector comprising the tTA transactivator.

The ordinary skilled artisan, desiring to use a cassette or vector with a splice acceptor site, positive/negative selection markers, a reporter gene and a tTA transactivator, would have been motivated to combine the teachings of Baetscher et al teaching the construction of gene trap vectors comprising a splice acceptor site, positive/negative selection markers, IRES elements, Stop codons, polyadenylation sequences and reporter genes, in various orders, with the teachings of Massie et al, teaching a cassette and then a vector comprising the tTA transactivator, since a vector with tTA in it is useful for functional studies and gene therapy applications. It would

have been obvious to one of ordinary skill in the art to incorporate tTA into the vector because the tTA system has been shown to be highly effective for the regulated expression of recombinant proteins. Given the teachings of the prior art and the level of the ordinary skilled artisan at the time of the applicant's invention, it must be considered, absent evidence to the contrary, that said skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

(10) Response to Argument

102(b) rejection –

Appellants argue that Baetsher does not teach a construct having a negative selection marker, positive selection marker, and a reporter gene under the control of a host cellular promoter. Instead Baetscher's constructs that include the selection markers and reporter gene include the promoter.

Appellants also argue that there are inconsistencies in the Examiner's position. According to Appellants, the Examiner states that the reporter is operatively linked to a promoter, however, then states that the reporter is under an endogenous promoter.

Lastly, Appellants argue that Baetscher fails to teach a vector with a negative selection marker, a positive selection marker, and a reporter gene with all three elements integrated into the genome of the cell and responsive to one or more endogenous regulatory elements.

Baetscher teaches integration of promoterless positive and negative selection markers (column 4, lines 4-11, lines 45-48, lines 55-60 and column 11, lines 25-31). The sequences were integrated to identify transcriptionally active endogenous promoters. Specifically, a vector containing promoterless markers, including positive and negative selection markers, is integrated into the genome of a cell. The markers are promoterless so that once integrated, they are under control of an endogenous regulatory element. Therefore, the positive and negative selection markers are integrated into the genome and responsive to an endogenous promoter.

One example of a nucleic acid construct used is a retroviral vector construct, which along with LTR elements (i.e., integration sequences) additionally contains selectable or assayable markers, including those useful in "fluorescence activated cell sorting". Thus, the general formula of a nucleic acid construct taught by Baetscher et al has the overall general formula of:

Splice acceptor---IRES---positive selection---negative selection---reporter.

However, several constructs are used, and this is just one example. The reporter gene is integrated into the genome. Appellants do not require that the reporter gene be promoterless, only that once it is integrated, it is responsive to an endogenous promoter. As discussed above, the constructs are integrated into the genome; therefore, even if the reporter was operatively linked to an exogenous promoter in the construct or vector, the reporter is now integrated, and therefore responsive to an endogenous promoter. Any promoter in the cell is an endogenous promoter. Also, the

reporter does not have to be responsive to the same endogenous promoter, since the claim language is "one or more endogenous regulatory elements."

Furthermore, the Appellants do not explicitly define "reporter" in their specification. Absent an explicit definition to the contrary, a "reporter" is any polypeptide sequence (as encoded by a polynucleotide sequence) that can be detected by conventional means. This includes colorimetric assays, bio- or chemiluminescence assays, as well as screening assays such as selection on a particular growth medium (such as a positive or negative selection marker). Because any polypeptide sequence can be detected by some means (e.g., by measuring its enzymatic activity, or detecting it with specific antibodies), any polypeptide meets the limitation of being a "reporter." The reporter could already be present (integrated) in the cell's genome, and therefore, under an endogenous promoter. The claims are product claims, so there is no active requirement for integration into the genome. "Cassette" is broad enough to include a nucleic acid sequence, so a gene, under an endogenous promoter, encoding a "reporter" would fit the language.

103(a) rejection –

Appellants argue that neither Baetscher nor the secondary references teach a construct, vector or cell with a negative selection marker, a positive selection marker, and a reporter gene with all three elements integrated into the genome of the cell and responsive to one or more endogenous regulatory elements.

As discussed above, Baetscher teaches a construct, vector or cell with a negative selection marker, a positive selection marker, and a reporter gene with all three elements integrated into the genome of the cell and responsive to one or more endogenous regulatory elements.

Appellants further argue that Massie et al do not each a transactivator polypeptide that is integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the cell.

Baetscher et al teach all of the elements set forth above. Massie et al teach a vector comprising the tTA transactivator. Massie et al also teach integration of tTA (see p. 2289 and figure 2, for example). Combined Baetscher and Massie teach a transactivator polypeptide that is integrated into the genome of a host cell and responsive to one or more endogenous regulatory elements in the cell.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michele K. Joike/

Examiner, Art Unit 1636

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